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Evaluation of the effect of bun/albumin ratio on in-hospital mortality in hypertensive COVID-19 patients

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Abstract. – OBJECTIVE: The impact of COVID-19 infection still continues all over the world and is an important cause of mortality. The mortality rate due to infection varies between 1-5%. The mortality rate is higher in those with cardiovascular risk factors, especially in cases with hypertension. Some studies have shown that blood urea nitrogen (BUN) and albumin levels are associated with worse prognosis in patients with COVID-19. In our study, we aimed to investigate whether the BUN/albumin (BAR) ratio has an effect on in-hospital mortality in hypertensive COVID-19 patients.

PATIENTS AND METHODS: A total of 800 hypertensive COVID-19 patients, (618 of whom were alive and 182 died) were included in our study. Patients with a history of heart failure, malignancy, acute coronary syndrome, and myocarditis were excluded.

RESULTS: The median age of the study population was 69 (60-77 IQR) years, and 305 (38%) of these patients were men. There was no statistically significant difference between the patients who died during follow-up and cases that remained alive in terms of comorbidities except chronic obstructive pulmonary disease (COPD) which was significantly lower in surviving group (p=0.014). Multivariable logistic regression analysis revealed that age [OR: 1.04, CI (1.01-1.06); p=0.002], male gender [OR: 1.85, CI (1.13-3.02); p=0.010], lymphocyte count [OR: 0.63, CI (0.40-0.98); p=0.038], SaO_2 [OR: 0.82, CI (0.79-0.85); p<0.001] and BAR level [OR: 1.09, CI (1.04-1.16); p=0.001] were independent predictors of in-hospital mortality. ROC analysis yielded that BAR is a better predictor of in-hospital mortality compared to albumin and BUN alone.

CONCLUSIONS: BUN, albumin, and BAR levels were found to be reliable predictors of in-hospital mortality in COVID-19 patients, and BAR was also found to be a more reliable predictor than BUN and albumin levels. Hypertension is one of the major risk factors for morbidity and mortality in COVID-19 and, BAR presents additional prognostic data in hypertensive COVID-19 patients that may direct physicians for treatment intensification.

Key Words:
Hypertension, COVID-19, In-hospital mortality.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by "severe acute respiratory syndrome coronavirus 2" (SARS-CoV- 2) and it recently led to a pandemic. COVID-19 affected millions of people and caused lots of morbidity and mortality worldwide. Respiratory tract involvement and cardiovascular manifestations account for the vast majority of COVID-19 related morbidity and mortality[1]. Hypertension is reported to be the most common comorbidity in hospitalized patients with COVID-19. It has been stated in many studies[2] that hypertension has unfavorable effects on the prognosis of COVID-19. It is postulated that SARS-CoV-2 enters the cells through angiotensin-converting enzyme 2 (ACE2) receptors, which are widely expressed in many organs, including the cardiovascular (CV) system, gastrointestinal tract, and respiratory system. Because the association between ACE2 expression and hypertension has been established, this high expression of a gateway for SARS-CoV- 2 might explain the high prevalence of hypertension in patients with severe COVID-19[1-3].

Blood urea nitrogen (BUN) is a frequently used biomarker to evaluate renal function and

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hypovolemia. BUN is one of the components of the CURB-65 score, which is used for the assessment of prognosis and need for hospitalization in cases with pneumonia[4,5]. Albumin is a negative acute phase marker and its level decreases in inflammatory situations such as infections. BUN/albumin ratio (BAR) has been shown to be a strong predictor of mortality in pneumonia and it is reported that albumin levels are also related to mortality in COVID-19[6,7].

With this study, we aimed to determine the relationship between BAR level and in-hospital mortality in the hypertensive sub-group of hospitalized COVID-19 patients.

Patients and Methods

Study Population

All of the hospitalized COVID-19 patients in the Gazi Yaşargil Training and Research Hospital were screened retrospectively and patients with hypertension and accessible data were enrolled. The study was staged compatible with the Declaration of Helsinki of 1975, as revised in 2013. This study was approved by the local ethics committee. COVID-19 diagnosis was confirmed with combination of a positive reverse-transcription polymerase chain reaction (PCR) test in addition to related signs and symptoms and/or specific findings on thoracic computed tomography. Data used in the study, including detailed physical examination findings, hematologic and biochemical laboratory values, hospital admission details such as including length of stay, admission to the intensive care unit, and the need of endotracheal intubation were obtained from hospital electronic databases. All patients were treated according to the National Health Ministry COVID-19 guidelines.

Hypertension diagnosis was made with a measured systolic blood pressure (BP) >140 mm Hg and/or a diastolic BP >90 mm Hg on at least 2 distinct assessments and/ or use of blood pressure lowering drugs before admission or during hospitalization due to COVID-19. The Beckman Coulter LH 780 hematology analyzer (Beckman Coulter, Brea, CA, USA) was used for the measurement of hematologic parameters and a Beckman Coulter LH 780 device (Beckman Coulter Ireland Inc, Kildare, IE) was used for biochemical parameters. All blood samples were drawn just after the admission to the emergency room. The nephelometry technique was used to measure serum BUN levels, and the bromocresol green method was practiced to evaluate serum albumin levels. The BAR value was calculated by dividing the BUN level to the level of albumin.

In addition, patients with a history of chronic kidney disease (CKD), heart failure, malignancy, and patients who developed acute coronary syndrome and myocarditis during hospitalization were excluded.

Statistical Analysis

The normally distributed numeric variables were expressed as mean±sd and non-parametric values were presented as median with interquartile range (IQR). The categorical variables were expressed as percentages. Categorical variables were assessed with Chi-square test, parametric variables were evaluated with Student *t*-test and Mann-Whitney U test was used for non-parametric variables. Logistic regression analysis was used for establishing in-hospital mortality related factors. A two-sided p-value < 0.05 was determined to be statistically significant. The data were analyzed using Statistical Package for Social Science® 24.0 (IBM, Armonk, NY, USA).

Results

A total of eight hundred cases with the diagnosis of hypertension who were hospitalized due to COVID-19 between April 2020 and October 2020 were included. Median age of the population was 69 (60-77) years and 38% of them (n=305) were male. Median creatinine value was 1.01 (0.80-1.36) mg/dL, BUN value was 42 (30-61) mg/dL and albumin level was 29 (25-35) mg/dL. Baseline characteristic features were presented in Table I.

In-hospital mortality occurred in 182 (22.7%) patients. Age, male gender ratio, percentage of chronic obstructive pulmonary disease and levels of creatinine, BUN, troponin, lactate dehydrogenase, white blood count, D-dimer, C-reactive protein (CRP) and BAR were significantly higher; while albumin and SaO_2 levels were distinctly lower in patients who died during hospitalization than counterparts who recovered from the disease and discharged after treatment (Table I).

Multivariable logistic regression analysis revealed that age [OR: 1.04, CI (1.01-1.06); p=0.002], male gender [OR: 1.85, CI (1.13-3.02); p=0.010], lymphocyte count [OR: 0.63, CI (0.40-0.98); p=0.038], SaO_2 [OR: 0.82, CI (0.79-0.85);

Table I. Baseline characteristics of the patients.

	Total (n = 800)	Survivor patients (n = 618)	Non-survivor patients (n = 182)
Age, (years)	69 (60-77)	67 (59-75)	74 (68-81)
Male sex, n (%)	305 (38)	202 (35)	103 (48)
CAD, n (%)	182 (23)	123 (21)	59 (27)
DM, n (%)	327 (41)	235 (40)	92 (43)
COPD, n (%)	67 (8)	40 (7)	27 (13)
CVE, n (%)	66 (8)	45 (8)	22 (10)
AF, n (%)	49 (6)	32 (6)	17 (8)
Serum creatinine, mg/dL	1.01 (0.80-1.36)	0.97 (0.80-1.25)	1.22 (0.85-1.64)
Urea, mg/dL	42 (30-61)	40 (29-54)	56 (37-79)
Albumin, mg/dL	29 (25-35)	30 (26-36)	26 (22-32)
Sodium, meq/L	136 (133-139)	136 (134-138)	136 (133-139)
Serum Potassium, meq/L	4.18 (3.77-4.49)	4.17 (3.77-4.50)	4.24 (3.77-4.78)
LDH, IU/L	320 (253-417)	301 (249-382)	376 (288-504)
Hemoglobin, g/dL	13.2 (12.0-14.2)	13.4 (12.1-14.3)	12.8 (11.8-14.1)
White blood cell count, 10^3//µL	7.20 (5.45-9.79)	7.03 (5.27-8.99)	8.38 (5.96-12.56)
Lymphocyte, 10^3//µL	1.05 (0.74-1.42)	1.12 (0.82-1.51)	0.85 (0.64-1.21)
Platelet count, 10^3//µL	205 (167-261)	204 (166-264)	207 (168-252)
Troponin, ng/mL	0.1 (0.1-0.1)	0.1 (0.1-0.1)	0.1 (0.1-0.1)
D-dimer, ng/mL	267 (175-416)	243 (166-374)	319 (212-587)
CRP, mg/dL	75 (36-133)	65 (28-115)	116 (63-166)
BAR (BUN/albumin ratio)	6.76 (4.67-10.41)	6.05 (4.35-8.72)	9.69 (6.41-14.01)
SaO_2, %	88 (80-91)	89 (85-92)	78 (70-83)

AF:Atrial fibrillation, BAR: BUN/albumin ratio CRP: C-reactive protein, DM: Diabetes Mellitus, CAD: Coronary Artery Disease, COPD: Chronic Obstructive Pulmonary Disease, LDH: Lactate dehydrogenase, CVE: Cerebrovascular event.

p<0.001] and BAR [OR: 1.09, CI (1.04-1.16); p=0.001] levels were independent predictors of in-hospital mortality (Table II).

ROC curve analysis was performed in order to establish sensitivity and specificity of BAR, albumin and BUN for predicting in-hospital mortality in study population (Figure 1). BAR value was demonstrated to be superior in predicting in-hospital mortality than other parameters by its higher sensitivity (65%) and specificity (65%) values (Table III).

Discussion

In this study, we determined that age, male gender, lymphocyte count, arterial oxygen saturation and BAR were independent predictors of in-hospital mortality in hypertensive COVID-19 patients. Moreover, we also found that BAR level was a stronger predictor than BUN and albumin levels.

There are several scoring systems used for estimating in-hospital mortality risk in patients with pneumonia. CURB-65, which is the most commonly used score in daily practice, is a five-

Table II. Multivariable logistic regression analysis of the parameters related to in-hospital mortality in hospitalized cases with COVID-19 and hypertension.

Variables	Multivariable logistic regression analysis	
	OR	CI 95%
Gender	1.85	1.13-3.02
Age	1.04	1.01-1.06
CAD	1.17	0.71-1.92
COPD	1.20	0.58-2.46
AF	1.02	0.41-2.51
White blood cell count	1.05	0.99-1.11
Lymphocyte count	0.63	0.40-0.98
Hemoglobin	0.97	0.90-1.10
Serum creatinine	0.82	0.49-1.39
SaO_2	0.82	0.79-0.85
CRP	1.01	0.98-1.04
LDH	1.00	0.98-1.02
D-dimer level	1.00	0.99-1.01
BAR	1.09	1.04-1.16
Troponin	1.19	0.73-1.94

AF: Atrial fibrillation, BAR: BUN/albumin ratio, CRP: C-reactive protein, OR: odds ratio CI: confidence interval, CAD: Coronary Artery Disease, COPD: Chronic obstructive pulmonary disease LDH: Lactate dehydrogenase

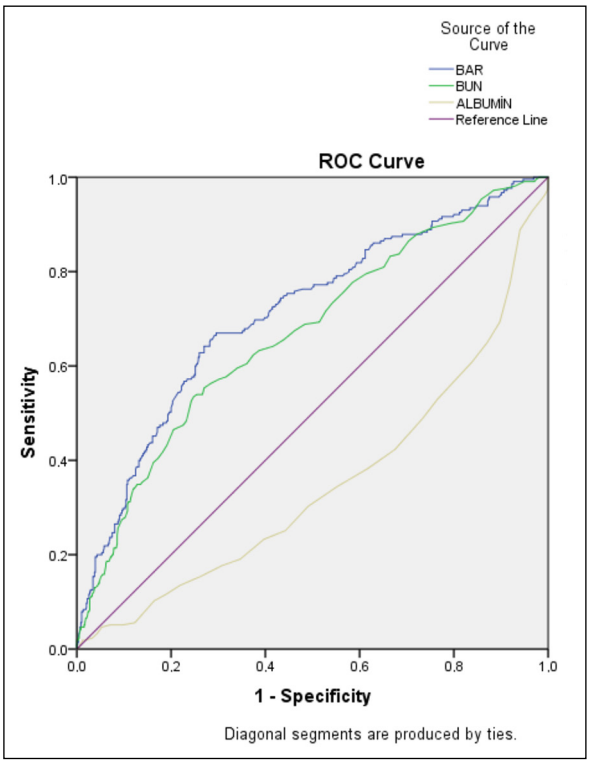

Figure 1. Area Under the ROC curve (AUC), sensitivity and specificity by the optimized cut-off points for BAR, BUN and albumin predicting in-hospital mortality.

point scoring system specifically developed for cases with community-acquired pneumonia, and it consists of urea >7 mmol/L (20 mg/dL), confusion, respiratory rate ≥ 30 breaths per minute, age ≥ 65 years and low blood pressure. However, CURB-65 score has many limitations decreasing its objectivity such as underestimating risk in younger patients and difficulty of neurological examination in elder patients with dementia[6]. Serum albumin has a significant role in maintaining colloid osmotic pressure, providing acid-base balance, and scavenging reactive oxygen species[6].

Albumin level decreases during inflammatory processes and it has both antithrombotic and anti-inflammatory effects. Albumin reduces releasing of thromboxane A2 which further converts prostaglandin H2 to PGD2. Moreover, it suppresses free radicals and exerts antioxidant effects. It has been reported that low albumin levels were related to unfavorable outcomes in COVID-19 patients[3].

Malnutrition is common in hospitalized patients and albumin is also an indicator of nutritional status beyond its negative acute phase marker role. It was reported in several previous studies[8-11] that malnutrition is frequent in COVID-19 cases. Reabsorption of urea increases in circumstances resulting in dehydration and hence, BUN level rises up. Dehydration occurs during respiratory tract infections due to several mechanisms including increased loss of water *via* respiratory tract, fever related peripheral vasodilation, increased sweating, and decreased water intake. There are several studies[12,13] establishing the relationship between low albumin and high BUN levels with poor outcomes in patients with pneumonia. Cheng et al[14] reported that BUN is an independent predictor of mortality in COVID-19 cases. Due to both albumin and BUN levels having prognostic effects on pneumonia, BUN/albumin ratio (BAR) was determined as a prognostic factor[15]. Ugajin et al[6] established that BAR was an independent predictor of 28 days mortality in cases with community acquired pneumonia; however, there is not any data about wether BAR is a prognostic factor or not in COVID-19 patients. In this study, we found that the BAR is a better prognostic marker than the individual albumin and BUN values in hypertensive COVID-19 patients.

Limitations

There are some limitations in our study. First of all, our study was designed as a single-center and retrospective study. However, the fact that our hospital is a pandemic center and has a higher patient burden significantly reduces the misclassification bias. Secondly, information about the medical treatment of the patients was not included.

Table III. AUC, sensitivity and cut-off values of BAR, albumin, and BUN in predicting in-hospital mortality.

Risk factor	AUC (95%)	Cut-off	*p*-value	Sensitivity (%)
BAR	0.710 (0.668-0.751)	7.43	< 0.001	67
BUN, mg/dL	0.668 (0.625-0.711)	8.91	< 0.001	63.3
Albumin, g/dL	0.349 (0.305-0.394)	2.75	< 0.001	42.3

AUC: Area under curve, BAR: BUN/albumin ratio, BUN: Blood urea nitrogen.

Conclusions

BUN/albumin ratio was reported to be associated with mortality in cases with community acquired pneumonia. This study demonstrated that BAR is also a prognostic factor for COVID-19, and it predicts in-hospital mortality.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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None.

Informed Consent
Informed consent for using their data was taken from all patients just before hospitalization.

Availability of Data and Materials
The data supporting this study's findings are available from the corresponding author, [E.B.], upon reasonable request.

Ethics Approval
Ethical approval was obtained from local ethical committee of Gazi Yaşargil Training and Research Hospital (Approval number: 464, Date: 15/05/2021).

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Authors' Contribution
M.O.: design of the study, collection of data, statistical analysis, writing, critical revision. Ö.B.: design of the study, approval of the final version of the manuscript. E.T.: collection of data. F.I.: writing, critical revision. Ü.İ.: statistical analysis. H.A.: collection of data. S.S.: approval of the final version of the manuscript. A.D.C.: reviewing the final version. R.T.: statical analysis. M.Ç.: manuscript preparation. Y.Z.Ş.: statistical analysis and writing. E.B.: reviewing the final version and submission.

References

1) World Health Organization. Clinical management of COVID-19: interim guidance, 27 May 2020. Geneva: World Health Organization; 2020.
2) Işik F, Çap M, Akyüz A, Bilge Ö, Aslan B, İnci Ü, Kaya İ, Taştan E, Okşul M, Çap NK, Karagöz A, Baysal E. The effect of resistant hypertension on in-hospital mortality in patients hospitalized with COVID-19. J Hum Hypertens 2022; 36: 846-851.
3) Saylik F, Akbulut T, Kaya S. Can Creactive protein to albumin ratio predict in-hospital death rate due to COVID-19 in patients with hypertension? Angiology 2021; 72: 947-952.
4) Küçükceran K, Ayranci MK, Girişgin AS, Koçak S, Dündar ZD. The role of the BUN/albumin ratio in predicting mortality in COVID-19 patients in the emergency department. Am J Emerg Med 2021; 48: 33-37.
5) Arihan O, Wernly B, Lichtenauer M, Franz M, Kabisch B, Muessig J, Masyuk M, Lauten A, Schulze PC, Hoppe UC, Kelm M, Jung C. Blood Urea Nitrogen (BUN) is independently associated with mortality in critically ill patients admitted to ICU. PLoS One 2018 25; 13: e0191697.
6) Ugajin M, Yamaki K, Iwamura N, Yagi T, Asano T. Blood urea nitrogen to serum albumin ratio independently predicts mortality and severity of community-acquired pneumonia. Int J Gen Med 2012; 5: 583-589.
7) Feng DY, Zhou YQ, Zou XL, Zhou M, Yang HL, Chen XX, Zhang TT. Elevated Blood Urea Nitrogen-to-Serum Albumin Ratio as a Factor That Negatively Affects the Mortality of Patients with Hospital-Acquired Pneumonia. Can J Infect Dis Med Microbiol 2019 16; 2019: 1547405.
8) Nazha B, Moussaly E, Zaarour M, Weerasinghe C, Azab B. Hypoalbuminemia in colorectal cancer prognosis: nutritional marker or inflammatory surrogate? World J Gastrointest Surg 2015; 7: 370-377.
9) Soeters PB, Wolfe RR, Shenkin A. Hypoalbuminemia: pathogenesis and clinical significance. JPEN J Parenter Enter Nutr 2019; 43: 181-193.
10) Li T, Zhang Y, Gong C, Wang J, Liu B, Shi L, Duan J. Prevalence of malnutrition and analysis of related factors in elderly patients with COVID-19 in Wuhan, China. Eur J Clin Nutr 2020; 74: 871-875.
11) Anderson CF, Wochos DN. The utility of serum albumin values in the nutritional assessment of hospitalized patients. Mayo Clin Proc 1982; 57: 181-184.
12) Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JT. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003; 58: 377-382.
13) Wernly B, Lichtenauer M, Vellinga NAR, Boerma EC, Ince C, Kelm M, Jung C. Blood urea nitrogen (BUN) independently predicts mortality in critically ill patients admitted to ICU: A multicenter study. Clin Hemorheol Microcirc 2018; 69: 123-131.
14) Cheng A, Hu L, Wang Y, Huang L, Zhao L, Zhang C, Liu X, Xu R, Liu F, Li J, Ye D, Wang T, Lv Y, Liu Q. Diagnostic performance of initial blood urea nitrogen combined with D-dimer levels for predicting in-hospital mortality in COVID-19 patients. Int J Antimicrob Agents 2020; 56: 106-110.
15) Huang D, Yang H, Yu H, Wang T, Chen Z, Liang Z, Yao R. Blood Urea Nitrogen to Serum Albumin Ratio (BAR) Predicts Critical Illness in Patients with Coronavirus Disease 2019 (COVID-19). Int J Gen Med 2021; 14: 4711-4721.